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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,355	03/22/2002	Paul David James Blackler	P32286	1395

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EXAMINER

MORRIS, PATRICIA L

ART UNIT PAPER NUMBER

1625

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/019,355	Applicant(s) BLACKLER ET AL.	
	Examiner Patricia L. Morris	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-33,36 and 37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-33,36 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 26-33 36 and 37 are under consideration in this application.

Drawings

The drawings are objected to because applicants have now inserted them in claims 28 and 29. Drawings must be on separate sheets and cannot be incorporated in the claims. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 26-33, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Again, there is a lack of description as to whether the compositions are able to maintain the compound in the crystalline form claimed. Applicants allege that the many references do not support the rejection and the examiner has failed to provide any scientific theory that supports the conclusions. This is certainly not true. The office action said that at a given temperature only one form is thermodynamically stable for an organic crystal. Note the teaching of *US Pharmacopoeia* if applicants prefers an additional reference.. Applicants have clearly failed to provide any **objective evidence that the instant polymorphs are indeed maintained in the compositions**. Hence, more references have been added to clearly show that applicants have failed to show the the compositions are able to maintain the crystalline form. Processing a compound into a pharmaceutical composition could create a different form than the crystalline form being claimed or even back to the compound itself. See pages 912-913 of *Habeblian*. *Doelker et al.* Abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or dosage form." *Taday et al.* p 831...Once in the desired crystalline form, the polymorphic form may be changed by incorrect storage or even during tablet preparation" and p. 836, figure 8, wherein the compound form four in the pharmaceutical composition resulted in similar spectra. The specification fails to describe the pharmaceutical compositions claimed in terms of their X-

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ray diffraction pattern or infrared spectrum data. The X-ray diffraction and Infrared spectrum data in the specification only pertains to the compounds rather than the compositions being claimed.

Chemical & Engineering News disclose that formulation of drugs or pharmaceuticals in its metastable forms, for example, on polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. Muzaffar et al., p. 60 states "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form." And p. 63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism. U.S. Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Applicants have failed to show that the metastable form will maintain its form after pharmaceutical formulation. Note Chemical & Engineering News.

The specification lacks description of how the pharmaceutical compositions can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Otsuka et al., p. 852 "...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process." Applicants are invited to note column 23 page 336 of Chakravarty et al. (supplied by applicants). Disclosure of X-ray diffraction patterns for pharmaceutical compositions comprising the crystalline forms are lacking in the specification.

Further, it is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if

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one is in possession of a particular crystalline form, no predictability can be found in such form will prevail in a pharmaceutical composition. See Chemical & Engineering News.

The specification has also not described how all the crystalline forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment and prevention of diabetes mellitus. In addition, it is well recognized in the art that the compound is given to the subject in a physiological environment, i.e., administered. There is no description or enabling support that the instant polymorph will be its physical form and biological activity results from the particular form instead of the "solution" state of the compound.

Also, the specification on page 3 recites that the instant compounds are made by known processes. However, different polymorphs cannot be made by the same method. There is no accurate way even to determine that a particular process will produce a crystalline form.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or

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use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention

The nature of the invention is the preparation of novel crystalline forms of the instant salt and compositions and for treating diabetes mellitus.

State of the Prior Art

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Although identical in chemical composition, crystalline salts can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Additionally, solids may form solvates. Polymorphs tend to convert from less stable to more stable forms. No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best to work with the most stable polymorph, because it will not convert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News, page 33. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

The amount of direction or guidance and the presence or absence of working examples

Polymorphs often change into other forms during drug manufacture into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the compositions and pharmaceutical compositions.

Further, the specification fails to show that the instant compounds treat diabetes mellitus. As evidenced by the art of record, it is well known that polymorphs can convert to the original compound. Since only the thermodynamically stable form which can maintain its form after formulation, the office action stated that absent of such description of whether any metastable forms will spontaneously change into the thermodynamically form or whether any metastable forms will maintain its form after pharmaceutical formulation, the specification lacks description and enablement in view of the empirical nature of the art.

The breadth of the claims

The breadth of the claims are drawn to the specific crystalline forms and in addition to the pharmaceutical compositions and the method of treating diabetes mellitus.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification. There is also lack of guidance as to whether the instant compounds rather than the original compound treats diabetes mellitus.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of

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unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression “substantially” in claims 28 and 29 is indefinite to its meaning. This rejection is maintained in view of applicants’ arguments in the instant response that it is not necessary to know that the spectrum or pattern is identical to that of a reference spectrum. How does one know that the instant polymorph is not the same as those known in the art.

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The U.S. Court of Claims held to this standard in Lockheed Aircraft Corp. v. United States, 193 USPQ 449, AClaims measure invention and resolution of invention must be based on what is claimed.

The C.C.P.A. in 1978 held a that invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim. In re Priest, 199 USPQ 11, at 15.

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Conclusion

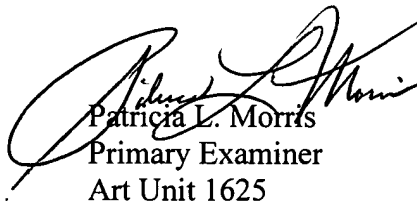
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688.

The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Patricia L. Morris
Primary Examiner
Art Unit 1625

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October 17, 2005